Physiology of the Liver & Biliary secretions

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ILOs

By the end of this lecture the student will be able to:

1. Explain the major functions of the liver with respect to synthesis, metabolism, detoxification, and excretion of hydrophobic substances.
2. Describe entero-hepatic circulation.
3. Describe the formation of bile & its constituents.
4. Explain its role in the excretion of cholesterol and bilirubin.
5. Explain functions of bile salts.
6. List functions of gall bladder.
7. Describe briefly bilirubin metabolism – jaundice.

Liver

Functions of the liver:

Liver is essential for life. It is the most important metabolic organ in the body.

The liver & gall bladder are accessory organs of the alimentary tract.

1. Metabolic Function:
   - A. Carbohydrate metabolism.
   - B. Fat metabolism.
   - C. Protein metabolism.

A. Carbohydrate metabolism.

The liver plays an important role in

1- Regulation of blood glucose concentrations “glucose homeostasis” by either adding or removing glucose from blood according to the body needs.

I. Well fed state:

- Glycolysis (ATP).
- Glycogensis (glucose storage as glycogen).
- Lipogensis.

II. Fasting state:

- Glycogenolysis.

- Gluconeogensis.

2 - Converts galactose & fructose into glucose.

B. **Fat metabolism**

1- Oxidation of fatty acids → energy.

2- Synthesis of

- Cholesterol *(80% is converted to bile salts).*
- Lipoproteins.
- Phospholipids.

3- Lipogenesis

- (fat synthesis from CHO & proteins).

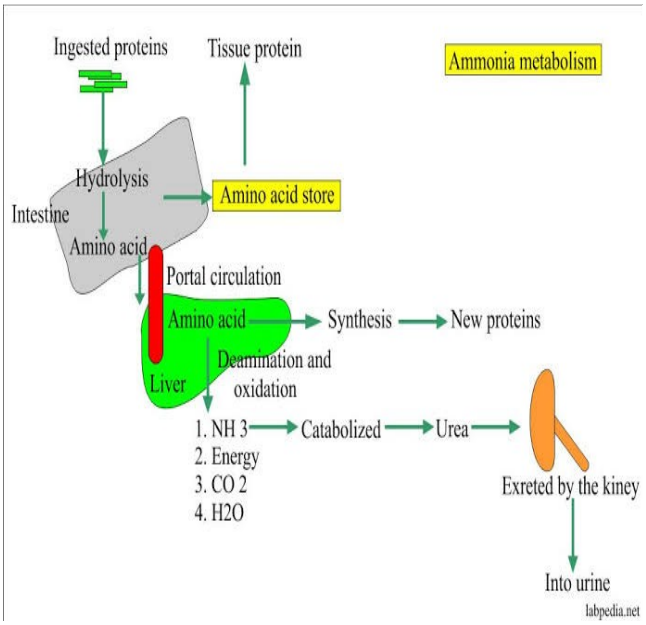
C. Protein metabolism

1- Deamination of amino acids → ammonia.

2- Transformation of ammonia (highly toxic) → urea (less toxic) to be excreted in urine.

3- Formation of uric acid which is the end product of nucleoprotein metabolism.

4- Synthesis of non - essential amino acids.

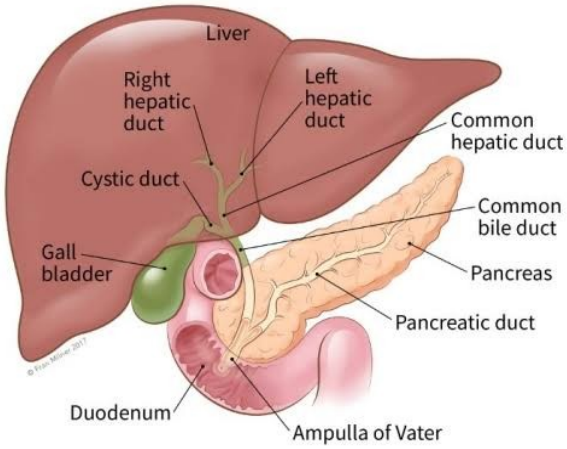


5- Synthesis of plasma proteins **except** gamma globulins.

2. Synthesis of …… plasma proteins:

- Albumin is quantitatively the most significant protein synthesized by the liver, and accounts for the majority of plasma oncotic pressure.
- Many of the products are acute-phase proteins, proteins synthesized & secreted into the plasma on exposure to stressful stimuli.
- Others are proteins that transport steroids and other hormones in the plasma, and still others are clotting factors.

- So, the only major class of plasma proteins not synthesized by the liver are the immunoglobulins “ ”.
- Hepatocytes form & secrete 600-1200 ml/day Bile (containing bile salts & bile pigments) → bile canaliculi → Stored in gall bladder →Emptied into the duodenal lumen with meals.



- Common hepatic duct + Cystic duct → Common bile duct (CBD).
- Common bile duct (CBD) joins Pancreatic duct → forming the ampulla of Vater which open in the duodenum “guarded by the sphincter of Oddi”.
- N.B.: In liver failure → Decreased plasma protein (albumin) → Decreased oncotic pressure → edema.

3. Blood reservoir:

- Liver stores about 200- 450 ml of blood in the hepatic veins and sinusoids.
- This amount can replace some of the blood lost in hemorrhage.

4. Detoxification of blood:

The liver has the ability to detoxify & excretes different substances as

a. Drugs & many toxins e.g. Penicillin, erythromycin, sulfonamides.
b. Hormones e.g. Aldosterone, cortisol, thyroxine, and estrogen.
c. Deamination of amino acids → Ammonia.

Ammonia → Urea.
Porphyrins → Bilirubin.
Purines, .. → Uric acid.

N.B.: In liver failure → increased levels of circulating ammonia → Hepatic encephalopathy.

In liver failure → increased levels of drugs → ?????.

Liver disease can result in the apparent over activity of some hormones.

5. Endocrinal function
   a. Secretes IGF-1 in response to GH → promotes growth.
   b. Secretes angiotensinogen to be changed to angiotensin I by renin
   c. Conversion of T3 toT4 by deiodination.
   d. Activation of vitamin D3 then, second activation in kidney → calcium absorption.
   e. Secrets Thrombopoietin → stimulates platelet production.
   f. Secrets Erythropoietin → stimulates RBCs production.

6. Liver is important for erythropoiesis
   - Forms 10% of erythropoietin.
   - Synthesizes the globin part of Hb.
   - Stores vitamin B12.
   - Stores iron "Blood iron buffer function".
   - Stores copper.
   - Erythrocytes formed in liver during fetal life.

   N.B.: In Liver Failure → anemia is a common finding in patients

7. The liver is important for blood clotting as
   A. The liver is the only site for formation of
      - Fibrinogen,
      - Prothrombin
      - Factor VIII
   B. In the presence of vitamin K, activation of factors
      - II , VII,
      - IX & X

   N.B.: In Liver Failure → Bleeding tendency is a common finding.

8. Storage function: The liver stores

- Glycogen.
- Fat.
- Vitamins (A, D & B12) (Liver stores can prevent deficiency for 10 months, 3-4 months, 12 months respectively).
- Iron.
- Copper.

9. Cleansing function (blood filtration):

- ♥ Kupffer cells: Are large phagocytic macrophages that lines hepatic sinusoids
- ♥ They cleanse & remove 99% of bacteria in the portal blood coming from intestine.

N.B.: in liver failure, systemic infection is common.

10. Production of acute phase proteins e.g C-reactive protein (important in inflammation).

11.

Bile

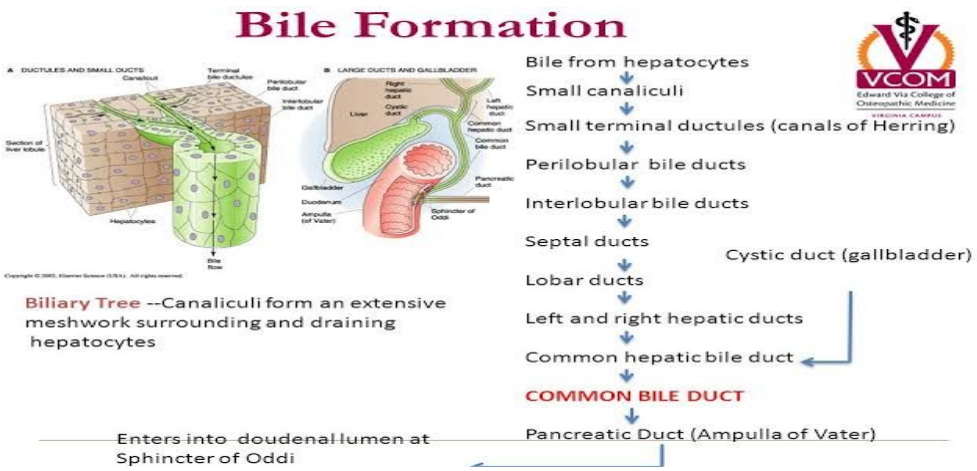
Bile: It is an aqueous, alkaline golden yellow juice that is secreted by the liver & stored in gall bladder.

- Volume: 600-1200 ml/day.
- pH: Alkaline.
- Composition of bile

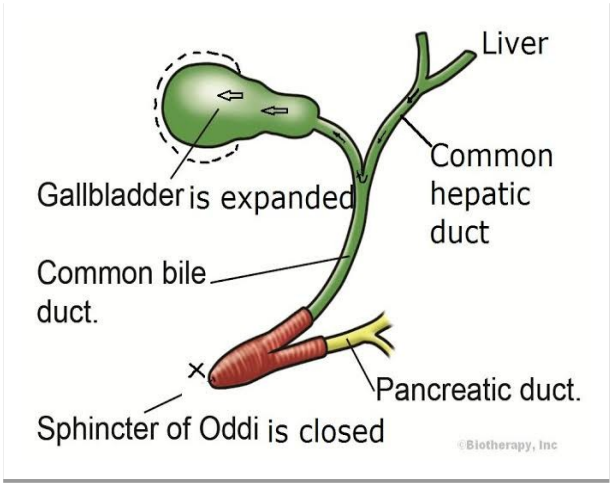
Organic constituents (2%)	**Inorganic constituents 0.5%**	Aqueous, alkaline secretion (97.5%)
- Secreted by hepatocytes. - Bile salts. - Bile pigments.	- Na, K, Ca & HCO3	- Secreted by duct cells. - Watery &

Bile formation: Bile is the secretion made up by the liver cells.

-The liver secretes about one liter of alkaline bile daily.



Mechanism of bile secretion:



During rest (in between meals):

- Sphincter of Oddi is contracted. So, "secreted bile by the liver passes to be stored in gall bladder "GB".
- GB concentrates bile by active reabsorption of Na^+ followed by Cl^- & H2O passively.

After meals

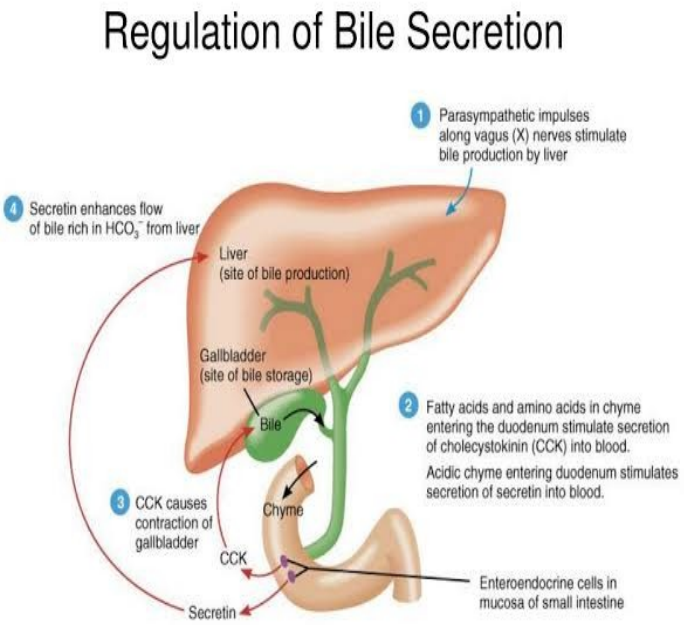
- 95% of bile salts are reabsorbed actively from the terminal ileum, then pass into the portal circulation back to the liver *(Enterohepatic circulation of bile salts).*

During meals

- Swallowing→ relax sphincter of Oddi.
- When food reaches intestine, CCK → contraction of GB→ evacuation of bile into duodenum.

Regulation of biliary secretion:

- *Chemical:* **Bile salts,** the most important stimulant of bile secretion by liver cells
- *Hormonal:* Secretin & CCK.
- *Neural:* Vagal stimulation during the cephalic and gastric phase of gastric secretion→



* Increases bile secretion rich in H_2O & $HCO3^-$.

* Contraction of gall bladder by releasing acetylcholine & Relaxation of sphincter of Oddi.

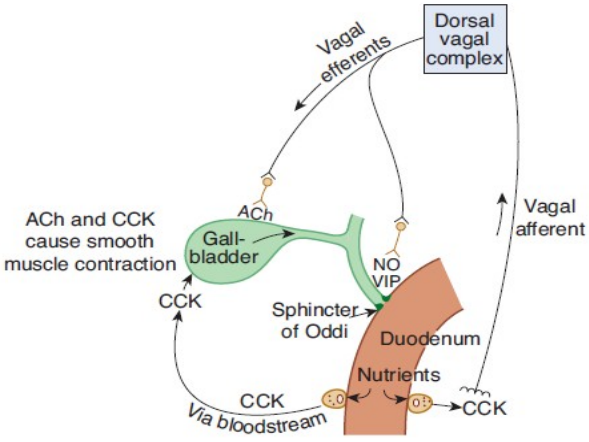
Hormonal

A. Secretin: Secreted by intestinal mucosa in response to acid chyme.

It stimulates bile secretion rich in H_2O &$HCO3^-$.

It is a choleretic.

B. CCK: Secreted by intestinal mucosa in response to Fatty acids& Amino acids.



It causes strong contraction of GB.

It is cholagogue.

Neurohumoral control of gallbladder contraction and biliary secretion

Choleretic: Increase bile production (increase water and bicarbonate content of the bile).

1- Bile salts (most potent).

2-Secretin hormone, released from S cells of upper intestinal mucosa.

3- Vagus nerve.

Cholagouge: Stimulate gall bladder wall contraction and relaxation of sphincter of Oddi.

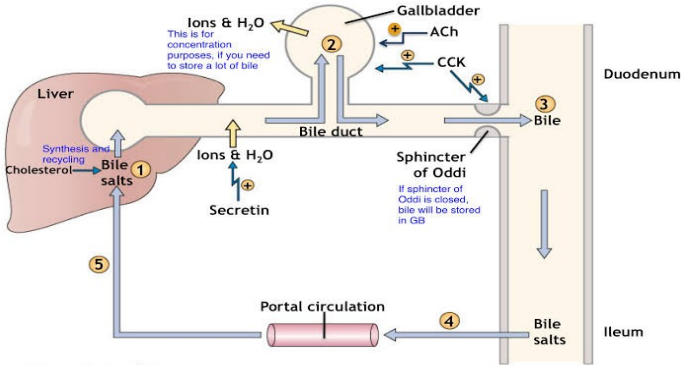
1-Cholecystokinin hormone, released from cells of upper intestinal mucosa.

2-Vagus nerve.

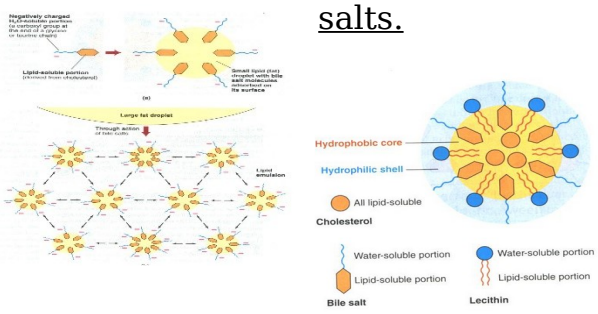
3- Magnesium sulfate.

Enterohepatic circulation of bile salts:

95 % of bile salts are reabsorbed by active transport from the terminal ileum into the blood & the remaining 5-10% enter the colon.



Functions of bile: Most of the functions of bile are due to the bile salts.



1. Digestive function: - Bile salts play an important role in fat digestion. Emulsify large fat particles into smaller ones that can be attacked by lipase (detergent action).

2. Absorptive functions: - Bile salts play an important role in fat absorption. Help in the transport and absorption of fat (micellar formation).

3. Excretory functions: - Bile pigments are the major excretory products of the bile.

Other substances excreted in bile are: i. Heavy metals like copper and iron. ii. Some bacteria like typhoid bacteria. iii. Some toxins. iv. Cholesterol. v. Lecithin. vi. Alkaline phosphatase.

4. Laxative action: - Bile salts act as laxatives by stimulating peristaltic movements of the intestine.
5. Antiseptic action: - Bile inhibits the growth of certain bacteria in the lumen of intestine by its natural detergent action.
6. Choleretic action: - Bile salts have the choleretic action = stimulate the secretion of bile from liver.
7. Maintenance of pH in gastrointestinal tract: - As bile is highly alkaline "Bicarbonate" , it neutralizes the acid chyme which enters the intestine from stomach. Thus, an optimum pH is maintained for the action of digestive enzymes.
8. Prevention of gallstone formation: - Bile salts Prevent precipitation of cholesterol by keeping them in solution (prevent gall stones).
9. Lubrication function: - The mucin in bile acts as a lubricant for the chyme in intestine.
10. Cholagogue action: - Bile salts act as cholagogues. It causes contraction of gallbladder and release of bile into the intestine indirectly by stimulating the secretion of hormone cholecystokinin.

Functions of the gall bladder:

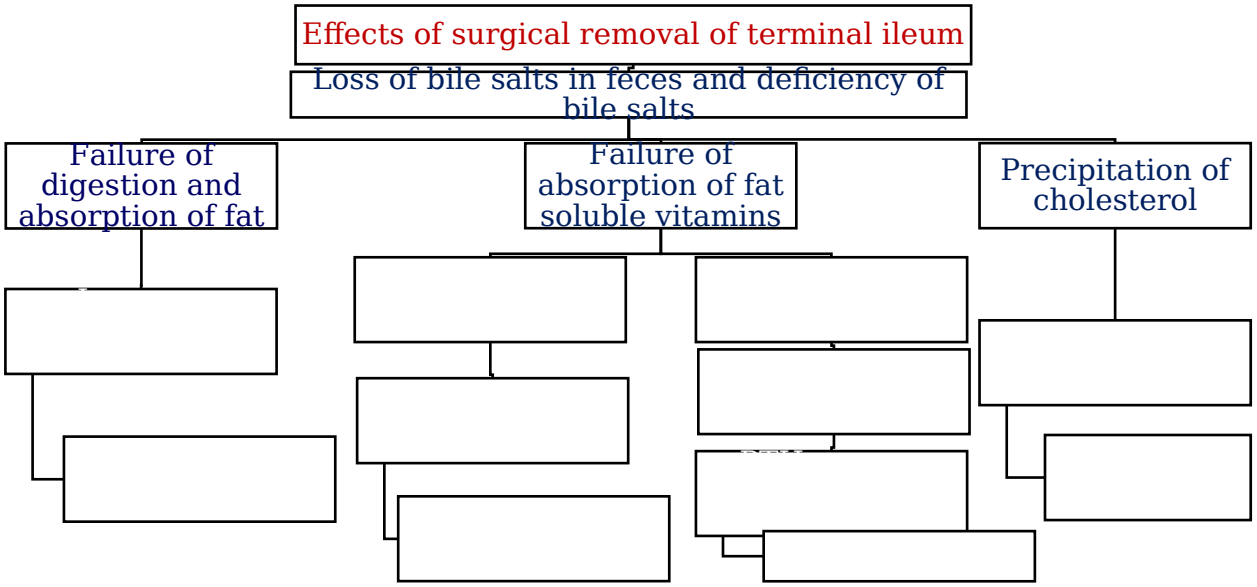
I. Storage of bile: Tonic contraction of sphincter of Oddi between meals → retrograde flow of bile from cystic duct to be stored in GB.
II. Concentration of bile: active reabsorption of Na^+ followed by passive reabsorption of water and most other electrolytes so the concentration of bile salts in GB increased 5-10 times. This concentration of bile prevent the rise in biliary pressure.

III. Acidification of bile: $Hco3^-$ reabsorption, this prevents ca^{++} precipitation and formation of gall stones.

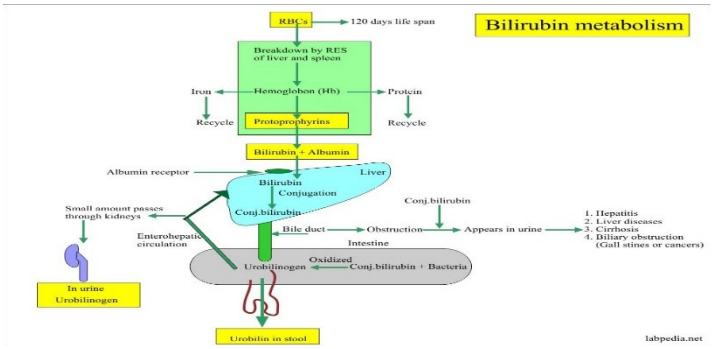
IV. Secretion of mucus (white bile): secreted by GB mucosa (protects GB from irritation by acidified concentrated bile, give bile semifluid consistency, in small intestine act as lubricant and buffer).

V. Evacuation of bile: Contraction of the wall and relax of the sphincter of Oddi stimulated by CCK and vagus.

Effects of surgical removal of terminal ileum



Bile pigments & Bilirubin metabolism:



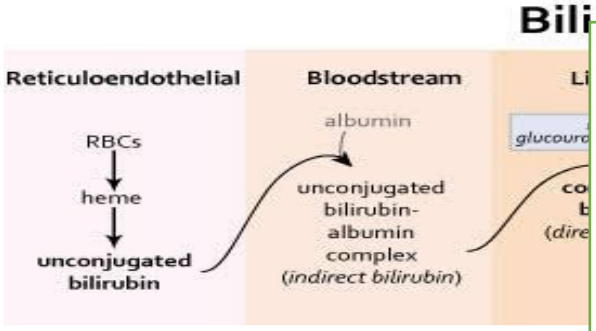
1. They are the end product for the breakdown of the haemoglobin content of the RBCs.
2. Haemoglobin is broken down into the haem and the globin parts.
3. Haem is further cleaved into iron and protoporphyrin, while the globin fraction is broken down into the constitutive amino acid which passes to the general protein metabolic pool.

4. The haem fraction is transformed into biliverdin then reduced into bilirubin.
5. Bilirubin is carried in plasma upon the plasma protein albumin; this fraction is called the free, indirect, the unconjugated or the Haembilirubin.
6. The free, the unconjugated or the **Haembilirubin** is uptaken by the liver cells to be conjugated with sulfuric or glucuronic acids forming the conjugated, the direct, the conjugated or the **Cholebilirubin.**
7. The liver excretes the **Cholebilirubin** through the common bile duct into the small intestine
8. In the small intestine, **Cholebilirubin** is converted into urobilinogen by the intestinal bacteria.
9. 75% of the intestinal **Urobilinogen** is transformed into another pigment; the **Stercobilinogen** which is excreted in the fecal matter to be oxidized on exposure to the air into a dark brown pigment called the **Stercobilin**, which gives the stool its dark brown coloration.

Enterohepatic circulation of urobilinogen

10. The remaining 25% of the Urobilinogen is reabsorbed from the intestine through the enterohepatic circulation where 20% of it is re-excreted into the intestine while just 5% is filtered through the kidneys into urine to be oxidized on exposure to air into **urobilin.**

Bilirubin



Conjugated	Unconjugated
❖ Cholebilirubin	• Hemobilirubin
❖ Direct bilirubin	• Indirect bilirubin
❖ Water soluble	• Free bilirubin
❖ Loosely bound to albumin	• Insoluble in water
❖ Excreted in urine (small	• Tightly complex to albumin

Jaundice

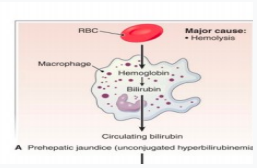
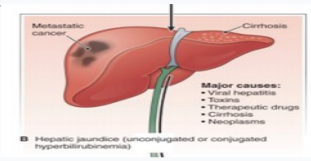
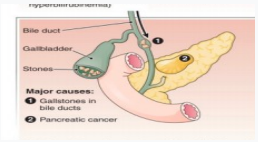
Yellowish coloration of the skin, eye sclera & mucous membranes due to excessive amounts of bilirubin in the blood.

- Normal plasma bilirubin is 0.5-1.2mg/dl (almost free bilirubin).

- Jaundice appears when bilirubin is above 1.5-2 mg/dl.

- Causes: ↑ free bilirubin (unconjugated hyperbilirubinemia) OR

↑ conjugated bilirubin (conjugated hyperbilirubinemia).

Category	
Pre-hepatic/ hemolytic	The pathology is occurring prior to the liver, due to either: A. Intrinsic defects in red blood cells. B. Extrinsic causes external to red blood cells. 
Hepatic/ hepatocellular	The pathology is located within the liver caused due to disease of parenchymal cells of liver. 
Post-hepatic/ cholestatic	The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage. 

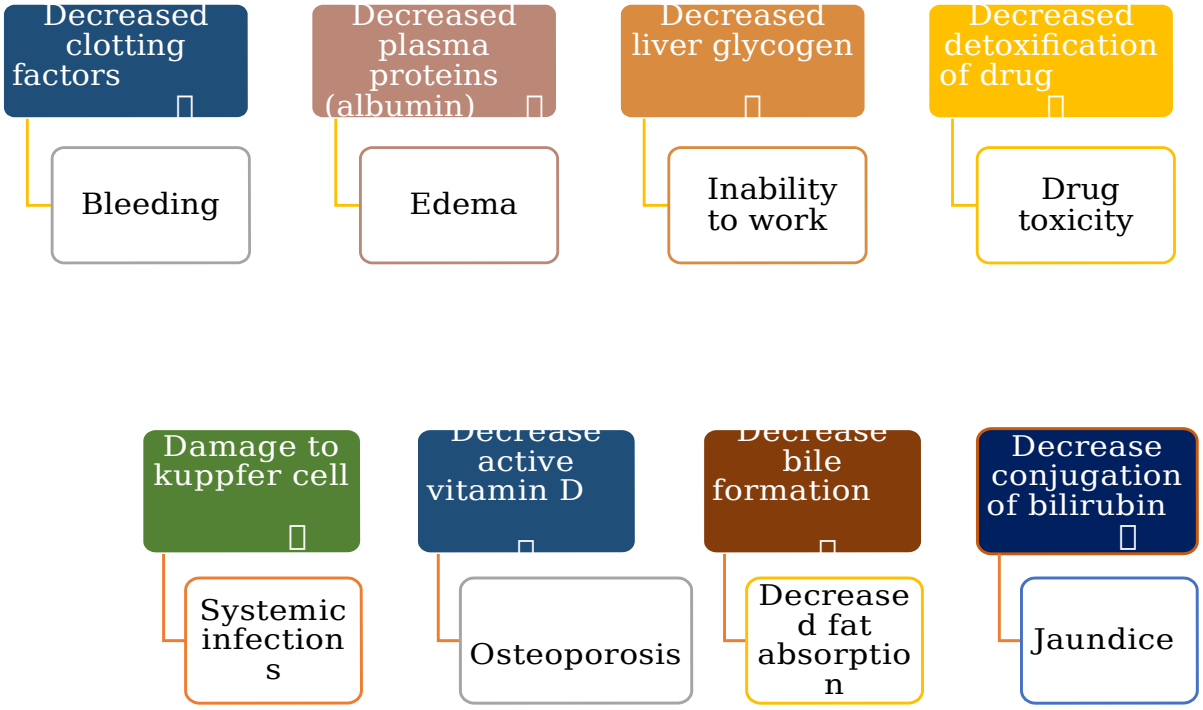
↑ Red blood cell destruction → Exceed the ability of hepatocytes uptake → Blood Free Bilirubin (Unconjugated) → Hemolytic Jaundice.

Liver Diseases → ↓ Conjugation & Excretion of Bilirubin → ↑ Blood Bilirubin (Unconjugated) → Hepatic Jaundice.

Common bile duct Obstruction → ↓ Bilirubin excretion → ↑ Blood Bilirubin (Conjugated) → Obstructive Jaundice.

	Hemolytic Jaundice	Hepatic Jaundice	Obstructive Jaundice
causes	Excessive RBCs break down	Liver disease hepatitis , toxic drugs	Obstruction of the common bile duct
Type of excess bilirubin in plasma	Free bilirubin	Free & conjugated bilirubin	Conjugated bilirubin
Depth of color	Mild	Moderate	Sever
Fat digestion	Normal	Moderately impaired	Markedly impaired
Liver functions	Normal	Markedly impaired	Moderately impaired
Urine color	Normal	Darker than normal	Dark brown
Stool color	Dark	Paler than normal	Very pale
Blood	Anemia, Reticulocytosis Cause of hemolysis	Moderate increase in cholesterol, alkaline phosphatase and bile salts	Marked increase in cholesterol, alkaline phosphatase and bile salts

Liver cell failure



Suggested textbooks:

Ganong's "Review of Medical Physiology", 25th edition, Section V gastrointestinal physiology, Chapter 26

Guyton and Hall "Textbook of Medical Physiology", 13th edition, Chapter 64

Sembulingam "Essentials of Medical Physiology", 6th edition, Chapter 41